NEW ZEALAND DATA SHEET

1 PRODUCT NAME

NICORETTE® 16hr INVISIPATCH®
10mg/16hr, 15mg/16hr, 25mg/16hr

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

NICORETTE® 16hr INVISIPATCH® patch is a transdermal delivery system for topical application, available in sizes of 22.5, 13.5 and 9 cm^2 each containing 1.75 mg/cm^2 of nicotine, releasing 25 mg, 15 mg and 10 mg respectively over 16 hours.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Transdermal patch. NICORETTE® 16hr INVISIPATCH® are semi-transparent, beige, imprinted, 9.0cm2, rectangular Transdermal Therapeutic System (TTS) with rounded corners, centrally located on a rectangular, aluminised and siliconised release liner.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Abrupt cessation of the use of tobacco-containing products following a prolonged period of daily use results in a characteristic withdrawal syndrome that includes four or more of the following: dysphoria or depressed mood; insomnia; irritability, frustration or anger; anxiety; difficulty concentrating, restlessness or impatience; decreased heart rate; and increased appetite or weight gain. Nicotine craving, which is recognised as a clinically relevant symptom, is also an important element in nicotine withdrawal.

Clinical studies have shown that nicotine replacement products can help smokers abstain from smoking.

4.2 Dose and method of administration

Could be used as a single treatment or in combination with either nicotine chewing gum or nicotine inhaler.

Children and Adolescents

NICORETTE® 16hr INVISIPATCH® patch should not be administered to individuals under 18 years of age without recommendation from a physician. There is limited experience of treating this age group.

Adults and Elderly

For Single Use
The recommended treatment programme for NICORETTE® 16hr INVISIPATCH® patch should occupy 3 months. The daily dose is one patch delivering 25mg, 15 mg or 10 mg nicotine as appropriate, with application limited to 16 hours in a 24 hour period in each case.

For heavier smokers (greater than 15 cigarettes a day) prepared to quit immediately: use patches in a 3 step program over 12 weeks applying: one 25mg/16hr patch/day for the first 8 weeks followed by one 15mg/16hr patch/day for the next 2 weeks (weeks 9 and 10) and one 10mg/16hr patch/day for a further 2 weeks (weeks 11 and 12).

For heavy smokers (greater than 15 cigarettes a day) not prepared to quit immediately: NICORETTE® 16hr INVISIPATCH® patch 25mg/16hr can be used while still smoking ad libitum during a 2-4 week preparation period. At the end of the 2-4 week period, smokers will stop smoking completely and continue using NICORETTE® 16hr INVISIPATCH® 25mg/16hr as per current dosing instruction.

For lighter smokers (less than 15 cigarettes a day) prepared to quit immediately: use patches in a 2 step program over 12 weeks applying: one 15mg/16hr patch/day for the first 8 weeks followed by one 10mg/16hr patch/day for the next 4 weeks (weeks 9 to 12).

For lighter smokers (less than 15 cigarettes a day) not prepared to quit immediately: NICORETTE® 16hr INVISIPATCH® patch 15mg/16hr can be used while still smoking ad libitum during a 2-4 week preparation period. At the end of the 2-4 week period, smokers will stop smoking completely and continue using NICORETTE® 16hr INVISIPATCH® 15mg/16hr as per current dosing instruction.

Patients should be reviewed at 3 months. Following this review, if abstinence has not been achieved, further courses of treatment may be recommended if it is considered that the patient would benefit.

NICORETTE® 16hr INVISIPATCH® patch should be applied to clean, dry intact areas of hairless skin, for example on the hip, upper arm, or chest. These areas should be varied each day and the same site should not be used on consecutive days.

There is no clinically significant difference in bioavailability of nicotine when the patch is applied to the hip, upper arm or chest.

After removal, used patches should be disposed of carefully.

Experience with treatment of nicotine dependence shows that success rates are improved if patients also receive supportive therapy and counselling.

Regular use of NRT beyond 9 months is not recommended. Some ex-smokers may need longer treatment with NRT to avoid returning to smoking.

When tobacco use ceases abruptly, the cravings can be intense and can be a cause of relapse to smoking. The use of patch concurrently with smoking for a few weeks prior to stopping helps prepare the body for quitting by gradually reducing the need to smoke. It provides a steady dose of nicotine which helps reduce conditioning and the reinforcing effects of smoking. The most intense cravings immediately after quitting are likely to be more manageable and the continued use of NICORETTE® 16hr INVISIPATCH® patch will manage cravings until it is no longer needed.

In Combination with Nicotine Chewing Gum, Nicotine Lozenge, Nicotine Quickmist Mouth Spray or Nicotine Inhaler

NICORETTE® 16hr INVISIPATCH® patch in combination with NICORETTE® 2mg Gum, NICORETTE® 2mg Lozenge, NICORETTE® 15mg Inhalator or NICORETTE® QuickMist Mouth Spray can be used if breakthrough craving is experienced or there is difficulty in controlling cravings for cigarettes. In people who have been unable to quit smoking using single NRT product, the combination is more effective than either product alone, increasing the patient's chances of successfully quitting.

Initial Treatment:

The NICORETTE® 16hr INVISIPATCH® patch should be applied daily to an intact area of the skin upon waking and removed at bedtime, and the NICORETTE® 2mg Gum, NICORETTE® 2mg Lozenge, NICORETTE® 15mg Inhalator or NICORETTE® QuickMist Mouth Spray should be used as required when cravings occur.

The initial treatment involves the addition of either NICORETTE® 2 mg gum, NICORETTE® 2mg Lozenge, NICORETTE® 15 mg inhaler or NICORETTE® QuickMist Mouth Spray to the patch. Gum may be taken as required to a maximum of 12 pieces a day when used in combination with the 25 mg/16 hour patch and 12 pieces a day when using the 15 mg/hr patch. Inhaler may be taken as required to a maximum of 6 inhaler cartridges a day when used in combination with the 25 mg/16 hour patch and 12 inhaler cartridges a day when using the 15 mg/hr patch (usually 2 – 3 inhaler cartridges will be adequate for effect). This full dose should be used for 12 weeks whereafter gradual weaning from the products should be initiated.

Weaning from Combination:

After the first 12 weeks of combination treatment it is suggested that either the 2mg gum/2mg lozenge, Quickmist Mouth Spray or 10 mg inhaler be continued while the lower strength patches are used over the next 4 weeks, then 2mg gum/2mg lozenge/10 mg inhaler, Quickmist Mouth Spray reduced; or the 2mg gum/2mg lozenge, Quickmist Mouth Spray or 10 mg inhaler be continued and

the patch discontinued followed by a gradual reduction in use of 2mg gum/2mg lozenge, Quickmist Mouth Spray or 10 mg inhaler.

Recommended Dosage:

Initial treatment				
Time period	**Patch**	**Gum or Lozenge 2 mg**	**Inhaler 10 mg**	**Quickmist**
First 12 weeks	1 patch 25 mg/16 hour per day OR 1 patch 15 mg/16 hour per day	Ad. libitum Recommended 5 - 6 gums or lozenges per day; maximum 12 gums or lozenges per day Ad. libitum Recommended 5 - 6 gums or lozenges per day; maximum 12 gums or lozenges per day	Ad libitum Recommended –2-3 cartridges per day; maximum 6 cartridges per day Ad libitum Recommended –2-3 cartridges per day; maximum 6 cartridges per day	Ad libitum at a dose of 1 or 2 sprays every 30 – 60 minutes. The maximum number of doses of mouth spray used in conjunction with the NICORETTE® 25 mg/16 hr INVISIPATCH® is 32 sprays per day (two sprays per hour for 16 hours).
Weaning - alternative 1				
Next 2 weeks	1 patch 15 mg/16 hour per day OR 1 patch 10 mg/16 hour per day	Continue to use gum or lozenge as needed	Continue to use inhaler as needed	Continue to use the Quickmist spray as needed
Following 2 weeks	1 patch 10mg/16 hour per day	Continue to use gum or lozenge as needed	Continue to use inhaler as needed	Continue to use the Quickmist spray as needed
Up to 12 months	----------	Gradually wean from gum or lozenge use	Gradually wean from inhaler use	Gradually wean from the Quickmist use
Weaning - alternative 2				
Up to 12 months	----------	Continue to gradually wean from gum or lozenge use	Continue to gradually wean from inhaler use	Gradually wean from the Quickmist use

4.3 Contraindications

NICORETTE® 16hr INVISIPATCH® patch is contraindicated in patients with generalised chronic dermatological disorders, such as psoriasis, chronic dermatitis or urticaria.

NICORETTE® 16hr INVISIPATCH® patch is contraindicated in non-tobacco users and in patients with known hypersensitivity to nicotine or any component of the patch.

NICORETTE® 16hr INVISIPATCH® patch is contraindicated in patients with Hypersensitivity to nicotine or to any of the ingredients in this product. NICORETTE® 16hr INVISIPATCH® patch, as with other nicotine containing transdermal patches should not be administered to children under 12 years of age.

4.4 Special warnings and precautions for use

Any risks that may be associated with NRT are substantially outweighed by the well established dangers of continued smoking.

Danger in small children
Doses of nicotine tolerated by adult and adolescent smokers can produce severe toxicity in small children that may be fatal. Products containing nicotine should not be left where they may be misused, handled or ingested by children. After removal, the patch should be folded in half, adhesive side innermost, and placed inside the opened sachet., or in a piece of aluminium foil. The used patch should then be disposed of carefully, away from the reach of children or animals. Suspected nicotine poisoning in a child should be considered a medical emergency and treated immediately.

Underlying cardiovascular disease
In stable cardiovascular disease NICORETTE® 16hr INVISIPATCH® patch presents a lesser hazard than continuing to smoke. However dependent smokers currently hospitalised as a result of myocardial infarction, severe dysrhythmia or cerebrovascular accident (CVA) and who are considered to be haemodynamically unstable should be encouraged to stop smoking with non-pharmacological interventions. If this fails, NICORETTE® 16hr INVISIPATCH® patch may be considered, but as data on safety in this patient group are limited, initiation should only be under medical supervision.

Diabetes mellitus
Patients with diabetes mellitus should be advised to monitor their blood sugar levels more closely than usual when NRT is initiated as catecholamines released by nicotine can affect carbohydrate metabolism.

Generalised dermatological disorders
Patients with chronic generalised dermatological disorders such as psoriasis, chronic dermatitis or urticaria should not use NICORETTE® 16hr INVISIPATCH® patch.

Erythema may occur. If it is severe or persistent, treatment should be discontinued.

Phaeochromocytoma and uncontrolled hyperthyroidism
Nicotine, from both NRT and smoking, causes the release of catecholamines from the adrenal medulla. Therefore, NICORETTE® 16hr INVISIPATCH® patch should be used with caution in patients with uncontrolled hyperthyroidism or phaeochromocytoma.

Epilepsy and seizures
Caution should be exercised in patients with a history of epilepsy or seizures during introduction of nicotine replacement therapy. Tobacco smoke contains substances – including nicotine – which act on brain receptors, and the changes in intake of these when switching from smoked tobacco to nicotine replacement therapy during quitting may affect seizure threshold.

Transferred dependence
Transferred dependence is rare and is both less harmful and easier to break than smoking dependence.

Continued smoking while using NRT
Patients must be made aware that should they continue to smoke whilst using NICORETTE® 16hr INVISIPATCH® patch they may experience increased adverse effects due to the increased levels of nicotine beyond those normally experienced with smoking alone. Such adverse effects include cardiovascular effects (e.g. angina, rapid or irregular heart beats).

Use in hepatic impairment
NICORETTE® 16hr INVISIPATCH® patch should be used with caution in patients with moderate to severe hepatic impairment as the clearance of nicotine or its metabolites may be decreased with the potential for increased adverse effects.

Use in renal impairment
NICORETTE® 16hr INVISIPATCH® patch should be used with caution in patients with severe renal impairment as the clearance of nicotine or its metabolites may be decreased with the potential for increased adverse effects.

Use in the elderly
A minor reduction in total clearance of nicotine has been demonstrated in healthy elderly patients, however, not justifying an adjustment of dosage.

Paediatric use
NICORETTE® 16hr INVISIPATCH® patch should not be administered to children under 12 years of age.

Doses of nicotine tolerated by adult and adolescent smokers can produce severe toxicity in small children that may be fatal. Products containing nicotine should not be left where they may be misused, handled or ingested by children.

Effects on laboratory test
No data available.

4.5 Interaction with other medicines and other forms of interaction

No clinically relevant interactions between nicotine replacement therapy and other drugs has definitely been established. However nicotine may possibly enhance the haemodynamic effects of adenosine i.e. increase in blood pressure and heart rate and also increase pain response (angina-pectoris type chest pain) provoked by adenosine administration.

Use in Magnetic Resonance Imaging
NICORETTE® 16hr INVISIPATCH® patch should be removed prior to undergoing any Magnetic Resonance Imaging (MRI) procedures.

Stopping smoking
Polycyclic aromatic hydrocarbons in tobacco smoke induce the metabolism of drugs metabolised by CYP 1A2 (and possibly by CYP 1A1). When a smoker stops smoking, this may result in slower metabolism and a consequent rise in blood levels of such drugs. This is of potential clinical importance for products with a narrow therapeutic window, e.g. theophylline, clozapine and ropinirole.

The plasma concentration of other drugs metabolised in part by CYP1A2, for example imipramine, olanzapine, clomipramine, fluvoxamine and caffeine may also increase on cessation of smoking, although data to support this are lacking and the possible clinical significance of this effect is unknown.

Limited data indicate that the metabolism of flecainide and pentazocine may also be induced by smoking.

4.6 Fertility, pregnancy and lactation

Nicotine passes to the foetus and affects its breathing movements and circulation. The effect on the circulation is dose-dependent. Smoking can seriously harm the foetus or infant and should be stopped. Pregnant or breast-feeding smokers should only use NICORETTE® 16hr INVISIPATCH® patch after consulting a health care professional. The risks for the foetus from NICORETTE® 16hr INVISIPATCH® patch are not fully known. The benefits of nicotine replacement therapy in pregnant women who cannot abstain without such therapy substantially outweigh the risk of continued smoking.

Nicotine passes into breast milk in small quantities that may affect the infant, even at therapeutic doses.

4.7 Effects on ability to drive and use machines

NICORETTE® 16hr INVISIPATCH® patch has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

NICORETTE® 16hr INVISIPATCH® patch may cause adverse reactions similar to those associated with nicotine administered by other means and are mainly dose-dependent.

About 20% of users experienced mild local skin reactions during the first weeks of treatment.

Clinical Trial Data

The safety of nicotine from clinical trial data is based on data on a meta-analysis of randomized clinical trials (RCTs) for the treatment of smoking cessation. Adverse Drug Reactions (ADRs) with patch formulations identified from clinical trials are presented below in Table 1.

Table 1. ADRs Reported with a Frequency ≥1% Identified from Meta-analysis of Clinical Trial Data with Nicotine Patch Formulations

System Organ Class	Active	Placebo
Preferred Term	N = 3917 (%)	N = 1366 (%)
Gastrointestinal Disorders		
Nausea[a#]	*Nausea*[a#]	*Nausea*[a#]
Vomiting[a]	*Vomiting*[a]	*Vomiting*[a]
General Disorders and Administration Site Conditions		
Fatigue[a*#]	0.4	1.0
Immune System Disorders		
Hypersensitivity[a*]	0.4	0.2
Nervous System Disorders		
Headache[a#]	5.2	6.1
Paraesthesia[a*]	0.4	0.3
Skin and Subcutaneous Tissue Disorders		
Pruritus	18.0	10.7

[a]:Systemic effects

*Although the frequency is <1% the PT occurred at a frequency ≥1% in any other formulation in which the PT was identified as a systemic ADR.

[#] Although the frequency in the active group is less than that of the placebo group, the frequency in the specific formulation in which the PT was identified as a systemic ADR was greater in the active group than the placebo group.

Post Marketing Data

ADRs first identified during post-marketing experience with nicotine are presented in Table 2. Frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 and < 1/10
Uncommon	≥1/1,000 and <1/100
Rare	≥1/10,000, <1/1,000
Very rare	<1/10,000
Not known	(cannot be estimated from the available data)

Table 2. ADRs Identified During Post-Marketing Experience with Nicotine Patch Formulations with Frequency Category Estimated from Clinical Trials

System Organ Class Frequency category	**Preferred Term**
Cardiac Disorders	
Uncommon	*Palpitations***
Uncommon	*Tachycardia***
Gastrointestinal Disorders	
Not known	*Gastrointestinal discomfort**
General Disorders and Administration site Conditions	
Uncommon	*Application site reactions*
Uncommon	*Asthenia***
Uncommon	*Chest discomfort and pain***
Uncommon	*Malaise***
Immune System Disorders	
Not known	*Anaphylactic reaction***
Musculoskeletal and Connective Tissue Disorders	
Uncommon	*Myalgia**
Not known	*Pain in extremity*
Nervous System Disorder	
Not known	*Seizure***
Psychiatric Disorders	
Uncommon	*Abnormal dream**,***
Respiratory, Thoracic and Mediastinal Disorders	
Uncommon	*Dyspnoea***

Skin and Subcutaneous Tissue Disorders	
Not known	*Angioedema***
Not known	*Erythema***
Uncommon	*Hyperhidrosis***
Common	*Rash***
Common	*Urticaria***
Vascular Disorders	
Uncommon	*Flushing***
Uncommon	*Hypertension***

*In vicinity/region of patch
**systemic effects
***systemic effect, identified only for formulations administered during night
reported the same or less frequently than placebo

Adverse reactions that may occur when using the combination treatment (patch and gum or patch and inhaler) only differ from each treatment alone in terms of local adverse events associated with the formulations. The frequencies of these adverse events are comparable to those reported for each product used alone.

Reporting Suspected Adverse Events
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Excessive use of nicotine from either nicotine replacement products and/or smoking might cause symptoms of an overdose.

Symptoms of overdosage are those of acute nicotine poisoning and include nausea, salivation, abdominal pain, diarrhoea, sweating, headache, dizziness, disturbed hearing and marked weakness. At high doses, these symptoms may be followed by hypotension, weak and irregular pulse, breathing difficulties, prostration, circulatory collapse and general convulsions.

Doses of nicotine that are tolerated by adult smokers during treatment may produce severe symptoms of poisoning in small children and may prove fatal. Suspected nicotine poisoning in a child should be considered a medical emergency and treated immediately.

In the event of overdose or poisoning activated charcoal should be given as soon as possible.

Administration of nicotine must be stopped immediately and the patient should be treated symptomatically. Activated charcoal reduces the gastrointestinal absorption of nicotine.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drug for treatment of addiction.

ATC code: N07B A01

Mechanism of action
NICORETTE® 16hr INVISIPATCH® patch is a treatment-aid in smoking cessation. Clinical studies have shown that nicotine replacement from nicotine containing products can help people give up smoking by relief of abstinence symptoms associated with smoking cessation.

Abrupt cessation of the use of tobacco-containing products following a prolonged period of daily use results in a characteristic withdrawal syndrome that includes four or more of the following: dysphoria or depressed mood; insomnia; irritability; frustration or anger; anxiety; difficulty concentrating, restlessness or impatience; decreased heart rate; and increased appetite or weight gain. Nicotine craving, which is recognised as a clinically relevant symptom, is also an important element in nicotine withdrawal.

Clinical studies have shown that nicotine replacement products can help smokers abstain from smoking by relieving these withdrawal symptoms.

Clinical trials
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In placebo-controlled double blind clinical studies, nicotine replacement with NICORETTE® 16hr INVISIPATCH® patch for periods up to 3 months increased the chances of successful abstinence without group support.

The post marketing, double blind, Collaborative European Anti-Smoking Evaluation (CEASE) study (n=3575 adult smokers smoking > 15 cigarettes per day) comparing an 8-week treatment period (plus 4 weeks taper with lower strength patches) with a 22 week treatment period (plus 4 weeks taper with lower strength patches) found no evidence of benefit from the longer treatment period. The primary outcome measure for this study was continuous self reported abstinence at 12 months (verified by CO monitoring).

5.2 Pharmacokinetic properties

General pharmacokinetic properties of nicotine

Nicotine is dibasic with a pKa1 of approximately 3 and a pKa2 around 8. Thus, nicotine is a weak base and its movement across cell membrane is pH dependent. It is easily soluble in both water and lipids depending on the degree of ionization. There are two stereoisomers of nicotine, (S)- and (R)-form, but it is only (S)-nicotine that is biologically active.

The pharmacokinetic studies of nicotine products have been performed in adult smokers. There are no differences in nicotine kinetics between men and women.

Absorption

Nicotine is released from the patch and absorbed through the skin. Vasodilatation caused by high ambient temperature and physical exercise increases absorption, whereas vasoconstriction caused by vasoconstrictor drugs decreases absorption.

During multiple dosing (i.e. one reference patch worn for 16 hours every 24 hours) there is no accumulation of nicotine in the body as a 16-hour application allows the nicotine plasma concentration to return to baseline prior to the next dosing interval.

When applied for 24 hours, additional nicotine was delivered (on average 3 mg for an original patch 15 mg). Bioavailability of absorbed nicotine is close to 100%.

Distribution

The volume of distribution following intravenous administration of nicotine, has been investigated in numerous studies. In six studies, mean values ranges between 2.2 and 3.3 L/kg.

Plasma protein binding of nicotine is considered to be low, about 5%. Therefore, changes in nicotine binding from use of concomitant drugs or alterations of plasma proteins by disease states would not be expected to have significant effects on the nicotine pharmacokinetics.

Metabolism
Results of pharmacokinetic studies suggest that nicotine metabolism and elimination are independent of the choice of nicotine formulation, and thus results from studies with intravenous administration of nicotine are used to describe distribution, biotransformation, metabolism and excretion.

The major eliminating organ is the liver, although the lungs and brain also metabolise nicotine to a small extent. The enzyme primarily involved in biotransformation of nicotine is CYP2 A6. Seventeen metabolites of nicotine have been identified, all of which are believed to be less active than the parent compound.

The primary metabolite of nicotine in plasma, cotinine, has a terminal half-life of 14 to 20 hours; the plasma concentrations of cotinine exceed those of nicotine 10-fold.

Excretion
Mean values of total clearance of nicotine between 66.6 and 90.0 L/h have been reported and the elimination half-life averages about 2-3 hours.
The primary urinary metabolites of nicotine are cotinine and trans-3-hydroxycotinine. On average 10-12% of the absorbed nicotine dose is excreted as cotinine and 28-37% of the dose is excreted as trans-3-hydroxy-cotinine. About 10-15% of nicotine is excreted unchanged in the urine. However, with low urine pH (below 5), as much as 23% of the nicotine dose was excreted unchanged.

There is a linear relationship between delivered amount of nicotine and C_{max}, AUC_t and AUC_∞.

Progressive severity of renal impairment is associated with decreased total clearance of nicotine. Nicotine clearance was decreased by 50% on average in subjects with severe renal impairment. Raised nicotine levels have been seen in smoking subjects undergoing hemodialysis.

In smokers with liver cirrhosis but only mild impairment of hepatic function (Child-Pugh score 5), the pharmacokinetics of nicotine is unaffected. However, in smokers with moderately impaired liver function (Child-Pugh score 7), total clearance has been reported to be reduced on average by 40-50%. There is no data about pharmacokinetics of nicotine in smokers with a Child-Pugh score exceeding 7.

Total clearance of nicotine is reduced in healthy elderly subjects, but deviations are variable and not considered sufficiently important to justify general age-dependent dose adjustments.

Pharmacokinetic Properties of NICORETTE® 16hr INVISIPATCH®
Following application of the NICORETTE® 16hr INVISIPATCH® patch to the upper arm or hip, approximately 95% of the nicotine released from the system enters the systemic circulation. The remainder of the nicotine released from the system is lost via evaporation from the edge. All patches are labelled by

the average amount of nicotine absorbed by the average patient over 16 hours.

Plasma levels of nicotine, obtained with patches, rise after application, and reach a maximum level after approximately 9 hours. The mean peak plasma level of nicotine achieved with the 25 mg/16 h patch is approximately 26.5 ng/mL. Nicotine kinetics is similar for application on the arm and hip.

After repeated applications, nicotine concentrations are not significantly higher than those after a single application.

Plasma nicotine concentrations show dose proportionality for the three patch doses (10, 15, 25 mg).

Pharmacokinetic Properties of the Combination of NICORETTE® 16hr INVISIPATCH® patch and NICORETTE® Chewing Gum and NICORETTE® 16hr INVISIPATCH® patch and NICORETTE® Inhaler, Respectively.
The plasma levels of nicotine when combining one 15 mg/16 hour patch and 2 mg chewing gum and one 15 mg/16 hour patch and 10 mg inhaler, respectively will depend on the number of gums chewed or inhaler cartridges used and the dosing interval.

Combination of NICORETTE® 16hr INVISIPATCH® patch and NICORETTE® Chewing Gum
A simulation of plasma concentrations shows that if one 25 mg/16 hour patch is applied in the morning and six 2 mg gums are evenly distributed over a 16 hour period according to the recommended dosage, a maximum plasma level of about –22.6 ng/mL will be reached at 9 hours.

Combination of NICORETTE® 16hr INVISIPATCH® patch and NICORETTE® Inhaler
Multiple dosing of the 10mg inhaler has been simulated with the scenarios of 10 and 20 minutes of usage. The highest value of single dose 25 mg/16 hour patch in combination with simulated multiple dose data of mean plasma concentrations of the inhaler when it is used for 20 minutes yields about 28.7 ng/mL (after 8.8 hours). When the inhaler is used for 10 minutes, the plasma values reach about 25,2 ng/mL after about 9 hours.

5.3 Preclinical safety data

In vitro and *in vivo* genotoxicity testing of nicotine has yielded predominantly non- genotoxic results. Some positive findings from *in vitro* and *in vivo* genotoxicity tests have been reported but investigations using regulatory accepted assays and protocols have shown no evidence of genotoxic activity at therapeutic doses.

Analysis of the results from long-term carcinogenicity assays data with nicotine or cotinine, major nicotine metabolite, predominately indicate nicotine does not have any significant or relevant carcinogenic activity.

General toxicology

Nicotine has oral and dermal LD_{50} in the range of 70 mg/kg. The general toxicity of repeated administration of nicotine is well known. Observations in chronic 2 year dosed feeding study in rats (5 mg/kg/day) showed no evidence of toxicity or overt behaviour and health including any tumor responses.

Genotoxicity

Nicotine showed negative results in *in vitro* tests but few *in vitro* and *in vivo* genotoxicity studies examining strand-breaking activity assessed by the comet assay, chromosome aberration or micronucleus formation gave positive results. However, the tested range is beyond the systemic nicotine levels achieved in humans by using nicotine products

Carcinogenicity

Long term animal studies with nicotine suggest that nicotine does not have any significant or relevant carcinogenic activity

Teratogenicity

In animal experiments nicotine induced maternal toxicity, fetal toxicity including post-implantation loss and growth retardation.

Fertility

In animal experiments, nicotine adversely affected spermatogenesis. To which extent female fertility is affected is not known.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Triglycerides, medium chain
Basic butylated methacrylate copolymer
Polyethylenterephthalate film (PET)
Acrylic adhesive solution
Potassium hydroxide
Croscarmellose sodium
Aluminium

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Each patch is packaged in a heat sealed multilaminate sachet. The sachet is composed of (from outside to inside of (printed) paper, PET, aluminium and Acrylinitril-copolymer or consisting (from outside to inside) of (printed) Paper, PET, aluminium, cyclo olefine copolymer coextrudate

Pack sizes:
10mg/16hr: 7, 14's, 28's
15mg/16hr: 7, 14's, 28's
25mg/16hr: 7, 14's, 28's

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

After application of a patch, as after removal, the hands should be thoroughly washed with water and dried after handling to avoid possible contact with sensitive areas such as the eyes.

NICORETTE® 16hr INVISIPATCH® patches are intended to be worn for 16 hours.

After removal, a used patch should be folded over and placed in its original pouch. It should then be disposed of immediately to prevent access by children or animals. As used patches contain some residual nicotine, both new and used patches must be kept out of the reach of children at all times.

In New Zealand, any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

General Sales Medicine

8 SPONSOR

JNTL Consumer Health (New Zealand) Ltd
507 Mt. Wellington Highway
Mt. Wellington, Auckland 1060

P.O. Box 62-185, Sylvia Park
Auckland 1644

9 DATE OF FIRST APPROVAL

18 March 2010

10 DATE OF REVISION OF THE TEXT

21 November 2022

Summary table of changes

Section changed	Summary of new information
All	Update to new Datasheet format. Addition of new packaging material. Addition of more restrictive safety and related statements. Updates to Adverse event data.
4.4, 4.8, 8	Addition of safety-related information on epilepsy and seizures. Revised sponsor name.